CO-ACTIVATORS AND CO-REPRESSORS IN GENE EXPRESSION

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National Institute of Diabetes and Digestive and Kidney Diseases
National Institute of Environmental Health Sciences
National Institute of Child Health and Human Development
National Institute on Aging
National Institute of Arthritis, Musculoskeletal, and Skin Diseases
National Institute of Mental Health

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

PURPOSE

This initiative stems from a recent NIDDK workshop in molecular endocrinology entitled: "Co-Activators and Co-Repressors in Gene Expression (December 15-16, 1998) and is designed to stimulate research that addresses the fundamental underlying mechanisms by which nuclear accessory proteins mediate signaling through hormone receptors at the level of the regulation of gene expression.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, CO-ACTIVATORS AND CO-REPRESSORS IN GENE EXPRESSION, is related to the priority area of diabetes. Potential applicants may obtain a copy of "Healthy People 2000" at http://www.crisny.org/health/us/health7.html.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and nonprofit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local

governments, and eligible agencies of the Federal Government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This PA will use the National Institutes of Health (NIH) research project grant (R01) and pilot and feasibility (R21) award mechanisms. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The duration of projects submitted in response to this PA may not exceed 5 years for R01s or 2 years for R21s. Applications for R21 grants must request no more than $100,000 direct costs in any one year.

Specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff. Refer to instructions under BUDGET INSTRUCTIONS below. Complete and detailed instructions and information on Modular Grants can be found at http://www.nih.gov/grants/funding/modular/modular.htm.

R01 applications that request more than $250,000 direct costs in any year must use the traditional budget format and PHS 398 application instructions.

Since NICHD and NIAMS do not routinely accept the R21, staff contact prior to submission is highly recommended.

RESEARCH OBJECTIVES

Summary

Co-repressors and co-activators represent classes of nuclear accessory proteins that include elements of the basal and regulated transcription machinery in cells. A recent NIDDK workshop in molecular endocrinology entitled: "Co-Activators and Co-Repressors in Gene Expression" (December 15-16, 1998) highlighted the importance of emerging information on the roles of nuclear accessory factors in the regulation of signaling at the level of transcription. Transcription

factors representing hormone receptors or other factors recruited by hormone receptors are responsible for enhancing and/or suppressing the expression of specific genes.

Background

The nuclear hormone superfamily comprises soluble hormones whose receptors are present in the cytoplasm and the nucleus of most cells. Members of this large hormone superfamily, such as the class I hormones, including adrenal glucocorticoids, mineralocorticoids, the sex steroids (estrogen, progesterone, androgen) and class II hormones, including, thyroid, vitamins A/D, PPAR, and retinoid X, have wide-ranging effects on metabolism, development, reproduction, sexual function, and behavior. The receptors for the nuclear receptor superfamily function primarily as transcription factors in the nucleus to either suppress or activate gene expression through effects on DNA transcription. In the absence of ligand, nuclear receptors, often bound as heterodimers (homodimers for the sex steroids) to hormone response elements (HREs) in the promoter regions of target genes, act to suppress transcription. In the presence of ligand, activation can occur.

Cell surface receptors (CSRs) are receptors whose ligand is extracellular, and binds to a receptor anchored in or spanning the membrane. Several classes of CSR exist; including the G-protein coupled receptors (GPCR), Ser/Thr kinase receptors, growth factor receptors, and cytokine receptors. All involve initiation of signaling cascades within the cell to amplify and effect the signal. End points of signaling through CSRs may also include change in gene expression through the activation of transcription factors.

Numerous recent findings have implicated several classes of nuclear accessory proteins which are recruited to the receptor dimer as co-activator or co-repressor complexes to suppress or activate gene expression at HREs for nuclear hormone superfamily, and other, receptors. Nuclear accessory proteins expressing histone acetyltransferase (HAT) or deacetyltransferase (HDAC) activities have been implicated in acetylation or deacetylation of core histones, thus altering the accessibility of DNA to elements of the RNA polymerase machinery. Other factors required for chromatin remodeling, and including methyltranferases, also alter accessibility, with potential effects on cell cycle control, mitosis, meiosis, and other functions of chromatin.
Still other factors serve to link the nuclear receptor when bound to HRE to the transcriptional machinery to complete the enhancer role of the nuclear hormone in regulation of gene expression. Still other transcription factors are activated as the end result of signaling cascades through CSRs. Co-activators and co-repressors serve integral functions in the formation of larger

scale complexes with HATs and/or HDACS that mediate the actions of transcription factors on gene expression.

Additional work presented at the "Co-Activator/Co-Repressor" workshop suggested a role for the relative affinity of binding of co-repressor versus co-activator complexes in determining whether a particular gene is activated or not in response to ligand. Further observations have pointed to mutations in nuclear accessory proteins and/or nuclear receptors as factors that can either cause hormone resistance or inappropriate gene expression. Fusion proteins, such as the AML-ETO fusion protein in acute myelogenous leukemia, have been implicated in tumorigenesis. In AML the mechanism of action appears to be recruitment of co-repressor complexes to block gene transcription relevant to differentiation of hematopoietic precursors. In another instance, mutations in one co-activator, AIB1, have been implicated in breast cancer. As a result, these factors have now become targets for therapeutic intervention. Thus, the specific objectives of this research solicitation include but are not limited to:

o Mechanism of action of nuclear receptors in the regulation of tissue-specific gene expression;

o Mechanism of signaling through cell surface receptors that result in recruitment and/or activation of transcription factors;

o Model systems that allow for study of in vitro or in vivo gene expression in target cells;

o Role(s) of nuclear accessory proteins in regulation of nuclear hormone action in target cells;

o Novel factor(s) associated with nuclear hormone action involved in disease genesis, including breast and prostate cancer, diabetes, neurodegenerative diseases, mental disorders, and osteoporosis;

o Analogs, agonists, or antagonists of nuclear hormones with potential effects on disease development and/or progression;

o Structural biology of the receptors focusing on interactions with other receptor interacting proteins, co-activators or co-repressors, the ligand, or HREs;

o Role(s) of heat shock, or other chaperone, proteins in regulating receptor function and/or interaction with ligands or nuclear accessory proteins;

o Signaling cross-talk between nuclear receptors and/or cell surface receptors and effects on regulation of gene expression and disease initiation/progression;

o Role(s) of hormones/nuclear accessory protein interactions in regulating events occurring during development, including differentiation of endocrine organs or tissues;

o Role(s) of hormones/nuclear accessory protein interactions on neural functions, brain development and behavior;

In addition:

The National Institute of Environmental Health Sciences (NIEHS) is interested in understanding how exogenous chemicals, including phytoestrogens, with hormonal activity alter the activity of endogenous hormone systems via mechanisms that disrupt cell signaling or cross talk between receptors, interact with specific receptor subtypes, or alter gene expression at the molecular level and the role of these changes in the initiation or progression of diseases.

The National Institute of Child Health and Human Development (NICHD) is interested in grants whose scope is relevant to issues of reproduction.

The National Institute on Aging (NIA) is interested in grants whose scope includes study of underlying mechanisms for age-related changes in gene expression mediated by hormonal signaling through receptors and nuclear accessory proteins; including age-related changes in responses involving nuclear accessory proteins with tissue-specific hormonal agonist or antagonist analogues.

The National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS) is interested in applications whose scope falls within the appropriate referral guidelines.

Finally, applicants are encouraged to discuss in the Significance Section the potential clinical relevance of their work.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that

inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This new policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which was published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide For Grants and Contracts, Vol. 23, No. 11, March 18, 1994, available on the web at: http://grants.nih.gov/grants/guide/notice-files/not94-100.html.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS.

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://www.nih.gov/grants/guide/notice-files/not98-024.html.

Investigators may also obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.4/98) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research, or may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301-435-0714, email: GrantsInfo@nih.gov.

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in þtime concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers, and Institute staff. The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below.

The program announcement title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit the signed, original, single-sided application, including the Checklist, along with five signed photocopies and five collated sets of appendix materials in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

The Center for Scientific Review (CSR) will not accept any application in response to this PA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

BUDGET INSTRUCTIONS

Modular grant applications will request direct costs in $25,000 modules up to a total direct cost request of $250,000 per year. Applications that request more than $250,000 in any year must use the traditional PHS 398 application instructions and not the instructions shown below.

The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Use a Modular Grant Budget Narrative page. (See http://www.nih.gov/grants/funding/modular/modular.htm for sample pages.)
At the top of the page, enter the total direct costs requested for each year.

o Under Personnel, list key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. (Address whether indirect costs for subcontracts are included in the total costs for the application. In general, indirect costs are not included in the total cost budget for R01s, etc.; however, if an absolute cap exists (e.g., centers), indirect costs are usually included in the total costs requested. Address whether the subcontract costs should be in modular form or rounded to the nearest $1000.)

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers to assess each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at http://www.nih.gov/grants/funding/modular/modular.htm

Complete the educational block at the top of the form page;
- List positions and any honors;
- Provide information, including overall goals and responsibilities on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations;

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. It is important to identify all exclusions that were used in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established Public Health Service referral guidelines. Applications will be evaluated for scientific and technical merit by scientific review groups convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second-level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewer will be asked to discuss the following aspects of the application in order to judge the likelihood that the

proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

o Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

o Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation: Does the project employ novel concepts, approaches, or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

o Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o Adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration to the proposed research.

o The adequacy of the proposed protection of humans, animals, or the environment, to the extent that they may be adversely affected by the project proposed in the application.

The initial review group will also examine the provisions for the protection of human subjects and the safety of the research environment.

o Availability of special opportunities for furthering research programs through the use of unusual talent resources, populations, or environmental conditions in other countries which are not readily available in the United States or which provide augmentation of existing U.S. resources.

AWARD CRITERIA

Applications will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

o Quality of the proposed project as determined by peer review;
o Availability of funds;
o Program priority.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic to:

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Direct inquiries regarding fiscal and administrative matters to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.847 (NIDDK), 93-846 (NIAMS), 93.866 (NIA), 93.113 and 93.115 (NIEHS), and 93.864 (NICHD). Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410, as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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